REMARKS

Applicants thank the Examiner for granting a telephonic interview with their representatives, Ying Li and Shilpi Banerjee, on January 5, 2005 and for her assistance during the interview. Applicants have amended the claims based on that interview, as further discussed below.

Claims 18-20, 23-27, 31-34, 37-43, 46-50, and 52 are pending in this application. Applicants respectfully request reconsideration of the application in view of the following amendments and remarks.

The Interview

During the January 5, 2005 interview, applicants and the Examiner focused their discussion on claim 18, which was representative of the pending claims. Claim 18 was directed to a method of genetically modifying human pluripotent hematopoietic stem cells with a viral vector, where the starting cell population was cultured in the presence of at least two cytokines – a mpl ligand such as TPO and a flt3 ligand (FL).

Applicants pointed out that, of all the references cited by the Examiner, only four of them relate to culturing hematopoietic cells in the presence of TPO and/or FL – Ku, Kobayashi, Ramsfjell, and Ohmizono. Applicants pointed out that the cells used in those references were committed progenitor cells and were at best multipotent. None of those four references taught or suggested culturing pluripotent hematopoietic stem cells in the presence of TPO and FL. Applicants explained that based on the definition in the specification (page 1, first ¶), pluripotent hematopoietic stem cells can differentiate into any hematopoietic cell type,

and are more primitive than committed progenitor cells or multipotent progenitor cells, which can differentiate only into limited hematopoietic lineages.

Applicants proposed amending the claims to require that the starting cell population be pluripotent stem cells that are $CD34^{+}Thy\text{-}1^{+}Lin^{-}$ and that can differentiate into any cell type. The Examiner agreed that the proposed amendment would overcome the outstanding prior art rejections and that she would enter it.

Claim Amendments

Accordingly, independent claims 18, 23, 37, and 52 are now amended to specify that the cells contacted with the viral vector are pluripotent human hematopoietic stem cells that are $CD34^{+}Thy\text{-}1^{+}Lin^{-}$ and can differentiate into any hematopoietic cell type. Support for this amendment appears in the specification at page 1, lines 4-11; and page 4, lines 27-30. Dependent claims 19, 20, 24-27 and 34 are amended to reflect the changes in the base claims.

Claims 18 and 52 are further amended to correct clerical errors – inserting the article "a" before "mpl ligand" and inserting a comma before "each ligand." Claims 23-25 and 39-42 are amended for conciseness. These amendments do not change the scope of the claims.

No new matter is introduced by the above amendments. In addition, all amendments set forth above raise no new issues that would require further consideration and/or search. Applicants submit that these amendments place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection. 37 C.F.R. § 1.116 (a).

Rejections under 35 U.S.C. § 103(a)

All of the pending claims – claims 18-20, 23-37, 31-34, 37-43, 46-50 and 52 – stand rejected as being obvious over Murray, Nakahata, Hoffman, Fei or Davis, in view of Ku, Kobayashi, Ramsfjell, Ohmizono, Szilvassy, Escary, or Bodine, and further in view of Tushinski, Fletcher, Bello-Fernandez, or Hatzfeld, and Hanenburg (Nature Medicine) or Hanenburg (Human Gene Therapy). Applicants respectfully traverse in view of the claim amendments.

The pending claims are directed to methods of genetically modifying human pluripotent hematopoietic stem cells with a viral vector, where the stem cells are cultured in the presence of at least two cytokines – a mpl ligand such as TPO, and a flt3 ligand (FL). Of all the references cited, only Ku, Kobayashi, Ramsfjell, and Ohmizono relate to culturing hematopoietic cells in the presence of TPO and/or FL.

As applicants noted during the January 5, 2005 interview, none of those four references teach that a mpl ligand such as TPO and FL can support proliferation of pluripotent hematopoietic stem cells without causing differentiation.[1] Rather, those references refer to multipotent cells that give rise to a limited subset of blood cell types.

For example, Ramsfjell makes a careful distinction between multipotency and pluripotency. While noting that its TPO-cultured cells were "multipotent," Ramsfjell admits that it failed to establish that those cells had lymphoid potential (p. 5176, left col., last full ¶).

[1] Applicants also note that Ku does not teach the combined use of TPO and FL. Ku refers to the combined use of sTPOR and FL. STPOR is a soluble receptor for TPO, and is not TPO.

That reference further states that it has yet to be seen that TPO can "expand the true long term reconstituting pluripotent stem cells" (p. 5176, right col., 1st ¶; emphasis added). Likewise, Kobayashi observes that "[b]oth FL and SF produced predominantly GM colony-forming cells in synergy with TPO . . . ." (p. 427, right col.). See also in applicants' June 30, 2003 and March 8, 2004 responses to office actions.

As previously discussed, the other cited references do not teach or suggest that TPO and FL can be used to expand pluripotent hematopoietic stem cells while retaining the cells' ability to differentiate into any hematopoietic cell type.

In conclusion, applicants respectfully submit that the proposed amendments place the claims in condition for allowance. The Examiner is invited to telephone the undersigned to discuss any issues remaining in this application.

Respectfully submitted,

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